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**John** [GB/GB]; Charter Way, Macclesfield, Cheshire SK10  
2NA (GB). **BOWEN, David, Brandon** [GB/GB]; Charter  
Way, Macclesfield, Cheshire SK10 2NA (GB).

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(74) Agents: **GAINEY, Laurence, David, Scott** et al.; AS-  
TRAZENECA, Global Intellectual Property, Mereside,  
Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

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(71) Applicant (for MG only): **ASTRAZENECA AB** [SE/SE];  
Sodertalje, S-151 85 (SE).

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(71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE,  
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VC, VN, YU, ZA, ZM, ZW only): **ASTRAZENECA UK**  
**LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater  
London W1Y 6LN (GB).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): **ROBERTS, Ronald,**

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(54) Title: LISINOPRIL COMPOSITIONS HAVING LARGE-PARTICLE DCPD

(57) Abstract: The present invention relates to a pharmaceutical composition comprising lisinopril and dibasic calcium phosphate dihydrate (DCPD), produced by a process comprising mixing lisinopril and DCPD with a specific surface area of less than 1.5 m<sup>2</sup>g<sup>-1</sup>. The use of large particle sized DCPD in a lisinopril formulation/composition has the effect of reducing the amount of the lisinopril degradation product DKP that is formed, thereby increasing the shelf-life of tablets formulated with the larger sized DCPD, particularly those with low doses of lisinopril.

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## LISINOPRIL COMPOSITIONS HAVING LARGE-PARTICLE DCPD

Background Of The Invention

The compound *1-(N<sup>2</sup>-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl)-L-proline*, having the  
5 generic name lisinopril, as well as therapeutically acceptable salts thereof, are described in  
United States patent serial No. 4,374,829 (Merck & Co. Inc.), incorporated herein by  
reference. In said patent the compound is described in Example 119, and is referred to as N- $\alpha$ -  
[1(S)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline. The divisional application of this patent,  
which has resulted in US patent No. 4,472,380, incorporated herein by reference, claims  
10 pharmaceutical compositions that include lisinopril pharmaceutical compositions. Lisinopril is  
a drug on which extensive clinical experience has been obtained. It is currently sold under the  
trademark ZESTRIL<sup>®</sup> by AstraZeneca or PRINIVIL<sup>®</sup> by Merck & Co. A combination of  
lisinopril and hydrochlorothiazide is sold under the trademarks ZESTORETIC<sup>®</sup> by  
AstraZeneca or PRINZIDE<sup>®</sup> by Merck & Co. ZESTRIL<sup>®</sup> and ZESTORETIC<sup>®</sup> are  
15 manufactured by wet granulation tableting using milled DCPD.

A typical lisinopril formulation consists of lisinopril dihydrate, which can be any dose  
from 1mg - 100mg, the fillers (diluents)- dibasic calcium phosphate dihydrate and mannitol,  
maize starch as a binder and disintegrant and magnesium stearate as a lubricant.

Lisinopril is a peptidyl dipeptidase inhibitor useful in treating cardiovascular diseases  
20 and disorders, such as hypertension and congestive heart failure (CHF) in mammals and  
especially in man. It inhibits the angiotensin converting enzyme (ACE) that catalyses the  
conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also  
stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased  
concentrations of angiotensin II which results in decreased vasopressor activity and reduced  
25 aldosterone secretion.

ACE is known to be present in the endothelium and increased ACE activity in diabetic  
patients which results in the formation of angiotensin II and destruction of bradykinin,  
potentiates the damage to the endothelium caused by hyperglycaemia. ACE inhibitors,  
including lisinopril, inhibit the formation of angiotensin II and breakdown of bradykinin and  
30 hence ameliorate endothelial dysfunction.

Dibasic calcium phosphate dihydrate (DCPD, CaHPO<sub>4</sub>·2H<sub>2</sub>O) is a diluent used in  
tablet and capsule formulations. It is used both as an excipient (diluent/filler) and as a source  
of calcium in nutritional supplements. It is used in pharmaceutical products because of its

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compaction properties, and the good-flow properties, particularly the coarse-grade material. Two main particle-size grades of DCPD are used in the pharmaceutical industry, milled and unmilled. The former material is typically used in wet-granulated or roller-compacted formulations whereas the latter coarse-grade material is typically used in direct-compression  
5 formulations.

Synonyms and trademarks for dibasic calcium phosphate dihydrate are: *Cafos*; calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; *Calstar*; *Calipharm*; dicalcium orthophosphate; *Difos*; DI-TAB; E341; *Emcompress*; phosphoric acid calcium salt (1:1) dihydrate; secondary calcium phosphate; calcium phosphate; and dicalcium  
10 phosphate, the latter two terms are commonly used generic terms in the pharmaceutical art.

Dibasic calcium phosphate dihydrate is white, odourless, tasteless, nonhygroscopic and stable at room temperature. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 100°C.

On long-term storage, when in the formulated product and particularly with low  
15 dosage formulations, lisinopril has a tendency to form diketopiperazine (DKP), a lisinopril degradation product or metabolite, which limits the shelf life for low dose formulations. The inventors have found a correlation between the amount and speed of DKP formation and the particle size of the co-formulated dibasic calcium phosphate dihydrate excipient.

It has previously been disclosed that when formulated as a tablet with large particle  
20 sizes of DCPD, aspirin has a reduced propensity to degrade to salicylic acid and acetic acid compared to aspirin formulated as a tablet with smaller particle sized DCPD (Landin et al., (1994) Int. J. Pharm. 107:247-249; Landin et al., (1995) Int. J. Pharm. 123:143-144). The mechanism for the degradation of aspirin to salicylic acid and acetic acid is hydrolysis (Leesen and Mattocks (1958) J. Am. Pharm. Sci. Ed., 67:329-333.). DCPD, which is known to readily  
25 dehydrate, provides water to promote the process. The poorer stability of tablets containing powdered material of DCPD as compared to aggregated material was attributed to a greater propensity of smaller particle size DCPD to lose more water (Landin et al., 1994, 1995, *supra*).

The breakdown of lisinopril to form DKP is, however, not a hydrolysis (the addition of  
30 water) but dehydration (loss of water) within the lisinopril molecule. Because the mechanism of action involved with aspirin and lisinopril degradation are completely different, it would not have been predictable that use of larger particle sized DCPD would also reduce the amount of lisinopril degradation.

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### Summary Of The Invention

The present invention relates to a composition comprising *1-(N<sup>2</sup>-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl)-L-proline* and processes for making the composition. *1-(N<sup>2</sup>-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl)-L-proline* is known under the generic name lisinopril. The  
5 novel composition is made with dibasic calcium phosphate dihydrate (DCPD, CaHPO<sub>4</sub>·2H<sub>2</sub>O) that possesses a low specific surface area of less than 1.5 m<sup>2</sup>g<sup>-1</sup> as determined by nitrogen adsorption (BET method). The use of large-particle DCPD in a lisinopril  
formulation/composition has the effect of reducing the amount of the lisinopril degradation product diketopiperazine (DKP) that is formed, which would increase the shelf-life of tablets  
10 formulated with the large-particle DCPD, particularly those containing low dosage amounts of lisinopril.

### Detailed Description Of The Invention

It has surprisingly been found that the lisinopril tablets formulated with large particle sized DCPD (unmilled) have a reduced tendency to form the lisinopril degradation product,  
15 diketopiperazine (DKP), particularly in low dosage lisinopril tablets. It is an object of the present invention to provide lisinopril tablets that have been made with larger particle sized DCPD than currently used, with the intention of reducing the amount of DKP degradation product that forms.

The invention is not limited by the tableting method. The large particle DCPD can be  
20 used to form lisinopril tablets by either the previously employed wet-granulated method or by a dry, direct-compression method, of the same type, familiar to those skilled in the art, that is used for other products. The amount of large particle DCPD can be as low as 30% (w/w) of the tablet to obtain the benefit of the invention.

Thus, according to a first aspect of the invention there is provided a pharmaceutical  
25 composition comprising lisinopril and DCPD, wherein the DCPD has a specific surface area prior to compacting or tableting of less than 1.5 m<sup>2</sup>g<sup>-1</sup>.

Thus, according to a further aspect of the invention there is provided a solid  
pharmaceutical composition comprising lisinopril, and an excipient, which comprises DCPD with a specific surface area of less than 1.5 m<sup>2</sup>g<sup>-1</sup> prior to compaction or tableting in an  
30 amount that is at least 30% (w/w) of the composition.

According to a further aspect of the invention there is provided a tablet, produced by either wet granulation tableting or dry direct-compression tableting comprising lisinopril, and an excipient, comprising lisinopril and an excipient which comprises DCPD with a

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specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$  prior to tableting in an amount that is at least 30% (w/w) of the composition.

According to a further aspect there is provided a tablet comprising lisinopril, an excipient comprising mannitol and DCPD, magnesium stearate, and maize starch.

5 According to a further aspect of the invention there is provided a pharmaceutical composition in tablet form containing an amount of lisinopril selected from 2.5mg, 5mg, 10mg, 20mg, 30mg and 40mg wherein the amount of lisinopril is expressed as the weight of anhydrous lisinopril (e.g. 30 mg Zestril tablets contain 32.67mg of lisinopril dihydrate).

In a preferred embodiment of each of the aspects of the present invention, the dibasic  
10 calcium phosphate dihydrate has a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ , more preferably less than  $1.25 \text{ m}^2\text{g}^{-1}$ , still more preferably less than  $0.9 \text{ m}^2\text{g}^{-1}$ , even still more preferably less than  $0.5 \text{ m}^2\text{g}^{-1}$ . In each instance the indicated specific surface area refers the specific surface area prior to any compaction or compression that is performed during tableting. In one  
15 embodiment the dibasic calcium phosphate dihydrate used in the invention has a specific surface area within the range of 0.2 and  $1.5 \text{ m}^2\text{g}^{-1}$ , preferably between  $0.3 \text{ m}^2\text{g}^{-1}$  and  $0.9 \text{ m}^2\text{g}^{-1}$ .

In further embodiments of the invention, the amount of DCPD is at least 50% (w/w) of the tablet, at least 60% (w/w) of the tablet and in the range of from 50% (w/w) to 70% (w/w) of the tablet. The excipient can further comprise at least 10% (w/w) mannitol.

The detailed compositions of specific formulations that are suitable for the present invention  
20 can be found in Bavitz, J.F., and Shiromani, P.K., 1986, Drug Dev. Ind. Pharm. 12, 2481-92 and in Shiromani, P.K., and Bavitz, J.F., 1988, Drug Dev. Ind. Pharm. 14, 1375-87.

The reduced amount of lisinopril degradation product is believed to be due to the reduced specific surface area of the DCPD diluent. Accordingly, it will be appreciated that the invention is not restricted to the situation wherein substantially all of the DCPD is within a  
25 narrow (but large) size range, but also covers large and small particle size mixtures of DCPD that possess the desired specific surface area. Such mixtures could, for example be formed by combining milled and unmilled DCPD. The SSA limitation is a measure of the total surface area which can therefore accommodate mixtures.

In one particular embodiment the lisinopril used according to the invention is lisinopril  
30 dihydrate. However, other solid forms of lisinopril, such as other polymorphs, solvates or monohydrates are also contemplated. Thus, by the term 'any form' we include, solvated and desolvated forms, crystalline forms and amorphous forms.

The present invention relies on the use of grades of DCPD that are commonly used in

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direct compression techniques thus, individuals or companies interested in preparing lisinopril tablets which routinely practice direct compression/compaction or dry granulation techniques, will particularly benefit from the present invention.

The inventors have discovered that the 2.5mg dosage tablets of lisinopril are  
5 susceptible to less DKP formation over time when DCPD with a lower specific surface area (SSA) than that conventionally used for wet granulation is used. It will be appreciated therefore, that because of the reduced propensity of the DCPD to dehydrate, there will be potential improvements in shelf-life of lisinopril tablets made with DCPD with a specific surface area less than  $1.5 \text{ m}^2\text{g}^{-1}$ , particularly of low dosage tablets such as 5mg or 2.5mg.  
10 According to a further aspect of the invention there is provided enhanced stability of 2.5mg tablets of lisinopril comprising using or incorporating dibasic calcium phosphate dihydrate with a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ . This can be effected by substituting unmilled DCPD for the conventionally used, milled DCPD.

The term stable as used herein, refers to the tendency to remain substantially in the  
15 same physical form for at least 6 months, more preferably at least a year, still more preferably at least 3 years, even still more preferably at least 5 years, when stored under ambient conditions ( $25^\circ\text{C}/60\%\text{RH}$ ) without external treatment.

The invention relies on the use of dibasic calcium phosphate with a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ . Some manufacturers of dibasic calcium phosphate will be able to  
20 provide the desired SSA of the product on demand. Others sell specific grades of dibasic calcium phosphate (i.e. Rhodia Di-Tab™ direct compression grade calcium phosphate dihydrate has a SSA of  $0.77 \text{ m}^2\text{g}^{-1}$ ; Landin et al., Int. J. Pharm. (1994) 107:247-249). The SSA of dibasic calcium phosphate dihydrate can be determined by the BET method using nitrogen adsorption in a Micromeritics Flowsorb II (Bunauer et al., (1938) J. Am. Chem. Soc.,  
25 60:309-319).

'Zestril' and 'Zestoretic' have received regulatory approval for use in the following indications:

#### Hypertension

'Zestril' is indicated in the treatment of essential hypertension and in renovascular  
30 hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.

'Zestoretic' is indicated in the treatment of hypertension.

### Congestive Heart Failure

'Zestril' is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis. High doses reduce the risk of the combined outcomes of mortality and hospitalization.

### 5 Acute Myocardial Infarction

'Zestril' is indicated for the treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

### Renal And Retinal Complications of Diabetes Mellitus

In normotensive insulin-dependent and hypertensive non-insulin-dependent diabetes mellitus patients who have incipient nephropathy characterised by microalbuminuria, 'Zestril' reduces urinary albumin excretion rate. 'Zestril' reduces the risk of progression of retinopathy in normotensive insulin-dependent diabetes mellitus patients.

According to the invention there is further provided a pharmaceutical composition comprising lisinopril, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients, produced by a process comprising admixing lisinopril and DCPD with a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ .

Compositions comprising other therapeutic ingredients are especially of interest in the treatment of hypertension, congestive heart failure, acute myocardial infarction and in renal and retinal complications of diabetes mellitus.

The invention also provides the use of lisinopril and dibasic calcium phosphate dihydrate with a specific surface area less than  $1.5 \text{ m}^2\text{g}^{-1}$  in the manufacture of a medicament for use in the treatment of a cardiovascular related condition, and in particular, a method of treating a hypertensive or congestive heart failure condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of a lisinopril composition produced by a process comprising admixing lisinopril and DCPD with a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ .

The invention also provides a pharmaceutical composition comprising lisinopril produced by a process comprising admixing lisinopril and DCPD with a specific surface area of less than  $1.5 \text{ m}^2\text{g}^{-1}$ , for use in treating hypertension, congestive heart failure, acute

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myocardial infarction and in renal and retinal complications of diabetes mellitus.

The invention also provides the use of a lisinopril composition produced by a process comprising admixing lisinopril and DCPD with a specific surface area of less than  $1.5 \text{ m}^2 \text{ g}^{-1}$  in treating hypertension, congestive heart failure, acute myocardial infarction and in renal and  
5 retinal complications of diabetes mellitus.

Any suitable route of administration may be employed for providing the patient with an effective dosage of drug comprising lisinopril according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like, e.g. enteric-coated capsules and/or  
10 tablets, capsules and/or tablets containing enteric-coated pellets of lisinopril. In all dosage forms lisinopril can be mixed with other suitable constituents. One route of administration is peroral using fast melt tablets.

The compositions of the invention comprise the compound of the invention. The compositions may be conveniently presented in unit dosage forms, and prepared by any  
15 methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of a pharmaceutical composition comprising lisinopril according to the present invention, in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age,  
20 body weight, and response of the individual patient.

In general, a suitable oral dosage form may cover a dose range from 0.5 mg to 150 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 1 mg to 60 mg.

Combination therapies comprising lisinopril according to the present invention and  
25 other active ingredients in separate dosage forms, or in one fixed dosage form, may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates, prokinetic agents, other antihypertensive agents, diuretics, digitalis, thrombolytics, aspirin and beta-blockers.

The invention is further illustrated, but in no way limited, by the following examples.  
30 EXAMPLES

Example 1

*Stability time course study of amount of DKP formation in 2.5mg lisinopril tablets containing different sources of DCPD.*



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Lisinopril tablets (2.5mg) were prepared with various types of DCPD according to standard wet granulation methods.

Stability data from Zestril tablets containing 2.5mg lisinopril dihydrate (Table 1) stored at 50 °C and different particle sizes of DCPD showed that degradation occurred rapidly in those tablets containing milled DCPD (low particle size, high SSA). It is interesting to note that larger particle sizes of DCPD confer stability to the formulation. Potentially giving an advantage of extended stability and thus longer shelf life to the product.

Degradation was determined using analytical high performance liquid chromatography (HPLC).

10

Table 1 Formation of diketopiperazine (DKP) in Zestril 2.5mg formulation at 50°C with different specific surface areas (SSA) of Dibasic Calcium Phosphate Dihydrate (DCPD)

| Source of DCPD     | SSA<br>(m <sup>2</sup> g <sup>-1</sup> ) | DKP (%) |         |
|--------------------|------------------------------------------|---------|---------|
|                    |                                          | 1 month | 2 month |
| Unmilled Calipharm | 0.40                                     | 0.50    | 0.97    |
| Kyowa              | 0.85                                     | 0.54    | 1.57    |
| Milled Calipharm   | 1.79                                     | 1.16    | 2.00    |

The enhanced stability, correlating with an increase in particle size, is due to particle shape of the primary particles, and is as a result of the crystal structure of DCPD. The crystal structure of DCPD consists of compact sheets composed of parallel chains in which calcium ions are co-ordinated by six oxygen atoms of the anions and by two oxygen atoms of the dihydrate waters (Curry and Jones. (1971) J. Chem. Soc A. 23:3725-3729). Two sheets form layers with water interacting between the sheets, this layer like structure is reflected in the plate like morphology of the crystals. Dehydration takes place through the edges of the plate and therefore milling the larger plates increases the surface area available for loss of water resulting in faster dehydration as particle size is reduced.

The stability of DCPD can be assessed by thermogravimetric analysis (TGA). The determination of the onset for dehydration of DCPD can be used as an indicator of the chemical stability of lisinopril in the formulation. The higher the temperature of dehydration of the first loss of water of DCPD then the more stable is the formulated product. Data for a number of sources of DCPD is shown in Table 2.

**Table 2** The effect of source of dibasic calcium phosphate dihydrate and the relationship between specific surface area (SSA) and the onset of the first water loss as measured by TGA.

| Source of DCPD       | SSA<br>(m <sup>2</sup> g <sup>-1</sup> ) | Onset for first water loss<br>(°C) |
|----------------------|------------------------------------------|------------------------------------|
| Emcompress           | 0.36                                     | 74.7                               |
| Calipharm (unmilled) | 0.40                                     | 72.1                               |
| Calipharm (milled)   | 1.79                                     | 56.6                               |
| Monsanto             | 1.87                                     | 65.5                               |
| Stauffer             | 2.10                                     | 59.2                               |

From the data in Table 2 it can be seen that sources of DCPD with specific surface areas less than 1.5 m<sup>2</sup>g<sup>-1</sup> have much higher onsets for the first loss of water of hydration. This reflects the same trend found for the stability of Zestril 2.5mg formulations (Table 1), in that, formulations containing DCPD having specific surface areas less than 1.5 m<sup>2</sup>g<sup>-1</sup> confer chemical stability to the formulation.

#### **Nitrogen Specific Surface Area**

The specific surface area of DCPD is determined by the BET method using nitrogen adsorption in a Micromeritics Flowsorb II. Samples were first degassed under a vacuum at 50°C for 24 hours.

#### **Thermogravimetric analysis**

Thermogravimetric analysis (TGA, Mettler TG50) was carried out on samples (10 - 30mg) over a temperature range of 25 - 300 °C and heating at 10 °C min<sup>-1</sup> using a nitrogen purge (100ml min<sup>-1</sup>)

#### **Example 2: Formulations**

Typical tablet formulations consist of:

- a drug (ranging from 1% – 50%);
- a filler (excipient, diluent), which typically can be dibasic calcium phosphate dihydrate or microcrystalline cellulose or lactose or mannitol;
- a binder, which typically can be polyvinylpyrrolidone (PVP) or hydroxy propyl methyl cellulose (HMPC) or microcrystalline cellulose or pre-gelled starch;
- a disintegrant, which typically can be crosscarmellose sodium or sodium starch glycolate or starch; and,

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a lubricant, which typically can be magnesium stearate and/or a glidant which is typically talc.

Formulations covering the extremes of 1% drug and 50% drug as an example are shown in Table 3

5

Table 3, Typical tablet formulations containing 1 and 50 % drug

| Ingredients  | % (w/w) | % (w/w) |
|--------------|---------|---------|
| Drug         | 1       | 50      |
| Filler       | 88      | 29      |
| Binder       | 5       | 10      |
| Disintegrant | 5       | 10      |
| Lubricant    | 1       | 1       |

In a preferred embodiment of the present invention a typical formulations containing lisinopril or lisinopril and hydrochlorothiazide as the drug (in amounts ranging from 0.5 mg –  
10 50mg) consists of large particle size dibasic calcium phosphate dihydrate as the major excipient, which can be 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% of the total tablet weight or any amount within the range of 30-95% of the total tablet weight.

The invention is particularly appropriate to lisinopril compositions (such as tablets) that comprise an amount of DCPD that is at least 30%, and preferably at least 50%, of the  
15 total composition (i.e. tablet) weight. Tablets that comprise DCPD as the main diluent in an amount of at least 50% of the total tablet weight are particularly preferred.

The detailed compositions of specific formulations that are suitable for the present invention can be found in Bavitz, J.F., and Shiromani, P.K., 1986, Drug Dev. Ind. Pharm. 12, 2481-92 and in Shiromani, P.K., and Bavitz, J.F., 1988, Drug Dev. Ind. Pharm. 14, 1375-87.

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**Claims:**

1. A solid pharmaceutical composition comprising lisinopril, and an excipient, which comprises dibasic calcium phosphate dihydrate (DCPD) in an amount that is at least 30%  
5 (w/w) of the composition, said DCPD having a specific surface area prior to any tableting of the composition of less than  $1.5 \text{ m}^2\text{g}^{-1}$ .
2. The solid composition of claim 1, which is a tablet produced by a wet granulation tableting process.  
10
3. The tablet of claim 2, wherein the DCPD has a specific surface area prior to tableting of less than  $0.9 \text{ m}^2\text{g}^{-1}$ .
4. The tablet of claim 3, wherein the excipient comprises DCPD in an amount that is at  
15 least 50% (w/w) of the tablet.
5. The tablet of claim 4, wherein the excipient further comprises mannitol in an amount that is at least 10% (w/w) of the tablet.
- 20 6. The tablet of claim 2, wherein the excipient comprises DCPD in an amount that is at least 50% (w/w) of the tablet.
7. The tablet of claim 6, wherein the excipient further comprises mannitol in an amount that is at least 10% (w/w) of the tablet.  
25
8. The solid pharmaceutical composition of claim 1, which is a tablet produced by a direct compression tableting process.
9. The tablet of claim 8, wherein the DCPD has a specific surface area prior to tableting  
30 of less than  $0.9 \text{ m}^2\text{g}^{-1}$ .
10. The tablet of claim 9, wherein the excipient comprises DCPD in an amount that is at least 50% (w/w) of the tablet.

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11. The tablet of claim 10, wherein the excipient further comprises mannitol in an amount that is at least 10% (w/w) of the tablet.
12. The tablet of claim 8, wherein the excipient comprises DCPD in an amount that is at  
5 least 50% (w/w) of the tablet.
13. The tablet of claim 12, wherein the excipient further comprises mannitol in an amount that is at least 10% (w/w) of the tablet.
- 10 14. The tablet of any one of claims 3, 4, 6, 9, 10 or 12, in which the lisinopril is lisinopril dihydrate.
15. The tablet of any one of claims 3, 4, 6, 9, 10 or 12, in which the amount of lisinopril is selected from the group consisting of: 2.5mg, 5mg, 10mg, 20mg, 30mg and 40mg.

## PATENT COOPERATION TREATY

## PCT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

|                                                                                          |                                                                                                                        |                                              |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Applicant's or agent's file reference.<br>100442/WO                                      | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |                                              |
| International application No.<br>PCT/GB 02/04292                                         | International filing date (day/month/year)<br>20/09/2002                                                               | Priority date (day/month/year)<br>24/09/2001 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K9/20 |                                                                                                                        |                                              |
| Applicant<br>ASTRAZENECA AB et al.                                                       |                                                                                                                        |                                              |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.



3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

EPO - DG 1

17.06.2003

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|                                                                                                                                                                                                                                             |                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of submission of the demand<br>17/03/2003                                                                                                                                                                                              | Date of completion of this report<br>26/03/2003                                                                                                       |
| Name and mailing address of the IPEA/<br> European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br>F RSTER W K<br>Tel. (+49-89) 2399 2828<br> |

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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International application No PCT/GB 02/ 04292

**I. Basis of the report**

The basis of this international preliminary examination is the application as originally filed.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability**

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 02/04292

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K38/55 A61K47/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                              | Relevant to claim No. |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | <p>WANG S L ET AL: "Thermal-Dependent dehydration process and intramolecular cyclization of lisinopril dihydrate in the solid state."</p> <p>CHEMICAL &amp; PHARMACEUTICAL BULLETIN. JAPAN DEC 2000, vol. 48, no. 12, December 2000 (2000-12), pages 1890-1893, XP001120078 ISSN: 0009-2363</p> |                       |

☐ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

28 November 2002

Date of mailing of the international search report

05/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Friederich, M

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